Contents of the manuscript

Introduction and general contexts

In the last thirty years, neurosciences have been very interested in the study of the correlation between sexual orientation (intended as a form of emotional, sentimental and/or sexual attraction of a person to another person regardless of the biological sex of belonging or his sexual identity) and certain neurobiological and neurophysiological components, capable of demonstrating the existence or otherwise of the direct relationship. Sexual orientation, properly so called, is therefore a lasting model towards another subject [1].

From the second half of the twentieth century, the first idea of “homosexuality” was declassified, moving from the psychopathological condition inherent to the sociopathic personality disorders of the 1954 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) to the sexual deviance of 1968, only to gradually become an ego-dystonic form of one’s own in 1974 sexual perception and finally a natural sexual orientation only in 1987 and in the revised version of 1990, being finally decriminalized reeds by the International Statistical Classification of Diseases, Accidents and Causes of Death (ICD) of 17 May 1990, [1], although psychoanalytic thinking was well oriented towards the opposite; in fact, homosexuality had hitherto been considered a “morbid obsession” (Charcot), a “sexual psychopathy” (von Krafft-Ebing), an “arrest of normal development” (S. Freud), a “narcissistic fixation” (Ferenczi), a “neurotic escape” (Adler) or a “paraphasic neurosis that originates from the conflict between instinct and inhibition” (Stekel) [2]. However, this evolution has certainly led to an opening towards social rights but also to a fluidity in sexual orientation, where the main problems emerge especially in the bisexual position [1]. The legal status of homosexual relationships varies enormously from one state to another and there still remain jurisdictions in which some homosexual behavior is considered a crime and punished with severe penalties (imprisonment), up to capital punishment
(death); this still happens in many African and Middle Eastern countries [3].

In addition to people who experience sexual and / or sentimental attraction for both people of the opposite sex and of their own sex (bisexuality in the strict sense), homosexual or bi-sexual behaviors can occur in many other cases, including [4].

Homosexual behaviors induced by the absence of other possibilities of sexual outlet (“situational homosexuality”), for example that which occurs in communities of people of one sex, such as prisons, barracks. It is also called “compensatory homosexuality” or, in the most ancient texts, pseudo--homosexuality (this last definition is now in disuse);

Child and adolescent homosexual behavior (or “sexual games”), (“adolescent homosexuality” or “transitory”);

Homosexual behavior most common in societies where sexual relations with people of the opposite sex are strictly reserved for adults (recourse to prostitution);

Homosexual behavior by people affected by some mental pathologies, such as to make the object of their erotic drives undifferentiated.

With reference therefore to bisexuality, understood as the choice of sexual orientation to bind sentimentally and sexually to both women and men, the discussion takes on broader and characterizing contours, precisely because of the apparently less defined and precise nature of the sexual orientation choice. The aforementioned fluidity on sexual orientation leads to rather bizarre decision-making developments and often motivated by unconscious dynamics not better identified even by the subjects [1, 5].

a) “bi-curiosity”, understood as a series of limited and sporadic behaviors about the desire to approach sexually individuals of the same sex, but who do not have the characteristic of persistence and recurrence over time;

b) “bi-chic”, a term describes people who engage in seductive relationships with both men and women with the intention of making people talk about themselves in a glamorous perspective;

c) “bi-permissive”, understood as the subject who does not actively seek sexual relations with people of a specific sex but who is “open”, that is, available to make new experiences;

d) “Bi- for pay-bi”: the term is applied to people who call themselves heterosexual but who engage in sexual relations with people of the same sex in exchange for money;

e) “Heteroflexibility”: this term of American origin, often used derisively or to deny one’s bisexuality, refers to a predominantly straight individual, but who can engage in a homosexual relationship occasionally because he is temporarily in a favorable context to it;

f) “Lesbians until graduation”: this term describes young British (and American) women who, during their year of study at university, engage in relations with other women, to then adopt, once they graduate, a strictly heterosexual attitude and end up getting married with a man.

Alfred Kinsey, author of the editorial work “Sexual behavior in the human male”, proposed a taxonomic scale, which suggested a value from 0 to 6, to describe those who were exclusively heterosexual (value 0), by those who considered themselves predominantly straight but with homosexual tendencies (value 1), with homosexual components (value 2), bisexual (value 3), mainly homosexual with heterosexual components (value 4), with heterosexual tendencies (value 5) and finally exclusively homosexual (value 6). However, this approach does not completely exhaust the complexity of sexual orientation. In the academic field, therefore, the issue of bisexuality as an innate orientation or consequence of factors is still strongly discussed [1].

Theoretical approaches

Sexual orientation is therefore commonly debated as a characteristic of the individual, as well as for biological sex, gender identity or age. However, this perspective is incomplete, since sexual orientation is always defined on the basis of relational terms and necessarily concerns relationships with other individuals. Sexual acts and romantic attractions are categorized as homosexual or heterosexual based on the biological sex of the individual involved in them, relative to the partners. Indeed, it is through performance - or the desire to lend - with another person that individuals express their heterosexuality, homosexuality or bisexuality. Thus, sexual orientation is fully connected to the intimate personal relationships that human beings form with others to meet their deepest sentimental needs for love, bond and intimacy. In addition to sexual behavior, these constraints include not–sexual physical affection between partners, sharing goals and values, mutual support and constant commitment. Consequently, sexual orientation is not merely a personal characteristic that can be defined in isolation. Likewise, one’s sexual orientation defines the universe of people with whom a person is able to find satisfying and fulfilling relationships which, for many individuals, comprise an essential component of personal identity [3].

There are essentially five sets of scientific theories on “differentiation of sexual orientation” [1].

Theories referring to “biological determinism”, according to which biological factors (in particular hormonal, neurological and genetic) determine or predispose sexual orientation.

Theories referring to the “domain of psychology”, which analyze sexual behavior and orientation in terms of mind or experiences and which relate sexual orientation to child psychic development.

Theories referring to the “domain of the psychiatric clinic”, and therefore homosexuality and bisexuality would be pathological forms.
Theories referring to the “domain of philosophy, sociology and anthropology”, therefore of an environmental matrix.

Theories referring to “the religious sphere”, meaning homosexuality as a form of deviance and sin, a vice determined by evil external forces.

There are many theoretical approaches regarding the development of sexual orientation involving the initial neural development of the fetus, with the proposed models illustrating exposure to prenatal hormones, maternal immunity and the instability of psycho-organic development itself. Other of the proposed factors include the control of the orientation by the genes, but certainly to date there are no definitive elements that can confirm the environmental conditioning as a direct and exclusive cause of the bisexual or homosexual condition [6], however, a recent study has shown that sexual orientation other than heterosexuality depends on a more or less precise combination of genetic and environmental factors: research shows that sexual behavior between subjects of the same sex is influenced by the multiple presence of different genes, at least five recognizable variants, which influence orientation for 25%, thus leaving the door open, for 75%, to the hypothesis of socio-cultural influences and preferences determined by environmental factors, and how these two elements affect and interact on subjective genetic influences [7].

From another point of view, however, it is known that the sexual dimorphism in the brain and the behavior between vertebrates are explained by the influence of the steroid androgens emitted by the gonads, as has been demonstrated for several animal models in the last decades. The prenatal androgen model of homosexuality wants to describe the neuro-evolutionary effects of fetal exposure to this class of hormones. Already in the mid-1980s, researchers Norman Geschwind and Albert Galaburda brought to the attention of the scientific environment the hypothesis that gay men had been exposed to high concentrations of androgens in the very early stages of gestation, also explaining their tendency to be more likely to be left-handed and by extension to all those hyper-masculinity traits observed within this population group. More recently, however, it has been argued that above all the temporal and local variations in the exposure of androgens to the brain still in the process of forming a fetus would be a decisive factor in the pathways that in a more advanced phase determine or not the gender identity in the as a whole and homosexuality in particular. We then moved on to the search for the “somatic markers” decisive for prenatal hormonal exposure which can be explored easily and in a completely not-invasive way in populations otherwise in the norm for endocrinology [6]. Various somatic indicators (including “2D: 4D finger ratios”, auditory evoked potentials, fingerprint pattern and blinking patterns) have been found to demonstrate changes in orientation based on orientation in healthy adult individuals [8,9]. Numerous other independent studies indicate that lesbian women have masculinized “digit ratios” and that in the majority of cases homosexuals reveal a relationship that can be either hyper masculinized or feminised [10-18]. Other evidence supporting the role played by testosterone and prenatal hormones includes observations of male subjects with congenital heart disease cloacal extrophy which at the time of birth were assigned to the female sex, but which only later were instead declared to be males. This fact supports the theory that increased prenatal testosterone dosage is crucial for the development of gender identity. Indeed women - whose mothers were exposed to diethylstilbestrol (DES) during pregnancy - showed higher rates of both bisexuality and homosexuality. These results seem to strengthen the prenatal androgen model: that is the not-typical exposure of the hormone is related to the subsequent development of human homosexuality [6].

Studies conducted on the elaboration of the central nervous system of auditory sensation, and whose main aspects have been linked to the exposure of prenatal androgens, to the stimulus test have shown that homosexual women have mostly masculinized responses, while on the other part gay men have hyper-masculinized responses [6].

The effect on the fraternal birth order also seems to have relevance. Studies conducted so far show that gay men have a higher percentage of older siblings when compared to heterosexuals, at least according to sexology expert Ray Blanchard. This consideration led to the discovery of the effect of the fraternal birth order, according to which the more siblings you have (from the same mother), the higher the possibility of expressing a conscious homosexual orientation that has become adults. Estimates indicate that there is an approximately 33% increase in the likelihood of homosexuality in a male child with an older brother [6] [19].

However, this effect is valid only for biological siblings, while the chances of male homosexuality are not increased by the number of older half brothers or siblings adopted. In fact, it is estimated that 1/7 of all homosexual males owe their sexual orientation to the effect of the fraternal birth order [20-23]. On the same theoretical trend, the tendency to write with the right hand would also seem interesting: the effect of the fraternal birth order increases the probability of homosexuality only in right-handed males. However, the effect applies only to right-handed homosexual males; on the other hand, the probability of homosexuality in left-handed or ambidextrous males does not increase [24].

Several studies, on the other hand, have demonstrated the absence of significant differences in the fluctuating asymmetry between heterosexuals and homosexuals, thus suggesting in fact that the homosexual one does not in fact represent a less than optimal phenotypic sexual orientation; on the contrary, it has been found that gay men and lesbian women show a less fluctuating asymmetry than heterosexual men or women, no more. In other words, heterosexuals have a weaker genomic ability than homosexuals in order to successfully buffer development and consequently obtain a normal phenotype in imperfect environmental conditions. In addition, “male to female” heterosexual transsexuals (MtF) showed greater fluctuating asymmetry than both homosexual and control groups, which shows that instability can explain variations in gender identity but not the orientation in itself [25-28].
Historical, anthropological and political profiles

Since the first draft of the DSM-I, in 1953, a strong debate was created in the scientific community about the correctness or otherwise of the presence of homosexuality within the psychiatric diagnostic manual. There were two main currents: the first denied presence because he considered it an alternative sexual orientation to heterosexuality, as otherwise the corrective hypothesis of morbid conditions would have to be considered (in essence, if we consider it a disease, we must consider a hypothesis of therapy and cure to solve it); the second considered any position other than heterosexuality pathological, according to a more biological direction, since the opposite sexes were able, in nature, to procreate, and therefore normality could only be this [3,4].

The (psychiatric) history of sexual deviance has often been subject to change by external social and political interventions, and not a clinical one. In reviewing the history of sexology, Havelock Ellis [29] and Magnus Hirschfeld [30], for example, stressed how it openly pursued an ethical and political aspect. In their view, the sexual instinct hasn’t changed much over time, but what has changed are the social reactions and the expression of these instincts. The historical study, therefore, simply served to record the progress made in attitudes towards unusual or bizarre forms of sexuality. But why then has deviant sexual behavior become a medical and psychiatric problem?

First of all, the pathologization of sexual deviance is not a new topic. Scientific literature on sexual behavior and the dangers of masturbation, prostitution and venereal diseases existed long before 1850 [31,32]. In 1761, the Swiss physician Samuel August Tissot published his “L’ananisme: Dissertation sur les maladies produites”, and many 18th–century enlighteners and thinkers, such as Thiry d’Holbach and Denis Diderot, agreed with him that masturbation and other types of not-reproductive sexual behavior (therefore not aimed at procreation), could cause serious risks to physical and mental health [33,34]. These writings, therefore, of a medical and philosophical nature, influenced the public understanding of unusual sexual relations, leading to a common perception and language that still influences judgment, creating the basis for the psychiatric approach of sexual deviance [35]. Furthermore, between the nineteenth and twentieth centuries, there was growing political concern on the vitality and health of nations and peoples on the part of utilitarians and nationalists. And therefore, to avoid the danger of a decline in births, politicians asked for the help of psychiatrists who, for various reasons, were taken seriously in their opinions contrary to sexuality not for procreative purposes. Prominent figures include French psychiatrists from the 19th and early 20th centuries [36] and anatomopathologists who considered sexual perversions as diseases of the genitals, caused by an anatomical anomaly [37]. Throughout the nineteenth century, then, and in particular due to the organological and phrenological influence of Gall’s theories [38,39], attention shifted to the link between “sexual desire” and “sexual instinct”, transforming perversions sexual in diseases of the sexual instinct [40–42]. The sexual perversions, at this point, formed a class of its own: a fourth class of pathologies of the sexual instinct, a character terrified by the deviation of the instinct from its natural purpose [43], also thanks to the sinful idea of the voluntary choice of the perverted to abandon themselves to these instincts [44]. This rigid view began to show cracks after the 1860s. More and more psychiatrists argued that perverse individuals had to be treated rather than punished. Desiring to improve their professional position [45], 19th century psychiatrists willingly assumed that, unlike diseases of the genital organs, perversions could and should have been treated psychologically. However, there was still consensus on Wilhelm Griesinger and his general claim that adequate therapy could only be identified through a healthy and convincing etiological diagnosis. This was thought for all mental pathologies, including sexual perversions [43]; for example, the French psychiatrists Charcot and Magnan believed that the psychogenesis of perversions implied that they could be treated with psychotherapy means [40].

Given that prophylaxis and treatment of perversions had to be based on a correct understanding of their etiology, how did mid-19th century psychiatrists identify the causes of sexual deviance? Different perspectives have been developed to explain these causes [46]. Most psychiatrists preferred a pathological perspective of the deviant condition, in which degeneration played a key role [47]. An essential element in most of these theories was the belief that ailments were hereditary and heredity, as Henry Maudsley said, was fate. Most theories of degeneration argued that aberrant sexual behavior, and in particular masturbation, could trigger or worsen hereditary vulnerability, thus inducing or accelerating a downward process in which all sorts of ailments would progressively and inevitably worsen during generations consecutive. Therefore sexual deviance was not considered only the result of degeneration, but also the cause of many other “degenerative” or “regressive” diseases, such as alcoholism, voluntary pauperism and moral madness [48]. These degenerative diseases of sexual instincts were often considered intimately intertwined with what we now call “gender deviance”, where a sign of feminization in men and / or masculinization in women could already be symptomatic, beyond the anamnestic picture [39]. The connection between gender problems, degeneration, and sexual deviance found its maximum connection in psychiatric theories on the nature and genesis of sexual behavior between people of the same sex, which for a long time was the most important category in many classifications of sexual deviance. In 1864, Karl Heinrich Ulrichs described how the “ournings” (ie men who were sexually attracted to him) were actually born with the spirit of the woman, while “urnindes” (ie women who were sexually attracted to women) had a male spirit trapped in a female body [49,50]. For most writers of the late 19th century, all genre variants of sadism and masochism inspired perspectives about degeneration, because they indirectly recalled a return to the brute evolutionary past.

From these positions the scholar Krafft–Ebing was involved in distancing himself, who saw perversions as “functional” deviations of the sexual instinct (“Geslechtstrieb”), which presented as an emerging force in puberty towards decline.
in old age [51]. Their location would be in the cerebral cortex, probably close to where the sense of smell resides and also believed that diseases of the sexual instinct were caused by cortical degeneration. Today we know that many of those intuitions were incorrect but this hypothesis opened the doors to the theses that saw perversions as the strong hereditary component, strengthened by masturbation. [52].

The most important change, partly prepared by other psychiatrists such as Jean–Etienne Esquirol, Carl von Westphal and Heinrich Kaan, came with the intuition that perversions were not only the result of a weak will or a defective anatomy, but rather, they were symptoms of a profound personality structure. The functional emphasis of these conditions and their psychological understanding led him to develop the opinion that perversions should be divided into “perversion acts” and “acts of perversity”. The perversions therefore became functional diseases, probably caused by a physical condition linked to the genitals or the nervous system and had to be sought in the more general picture of the patient’s personality: “In order to differentiate between the disease (perversion) and the vice (perversity) we must investigate the whole personality (...) and the original motive that leads to the perverse act”.

Krafft-Ebing thus maintained that perversions were about deriving sexual pleasure from imagination and fantasy, even in the absence of concrete realization of their fantasies. Krafft-Ebing thus distinguished four classes of sexual disorders, which he called “sexual neurosis”: the decrease in sexual appetite (“anesthesia”); its abnormal increase (“hyperesthesia”); its manifestation outside the normal biological period (“paradoxia”); the clinical perversions (“paresthesia” or “paraphilias”), on which psychiatry would have increasingly concentrated in the future [53].

Sigmund Freud, with great intuition, coined his sexual theory by drawing on dozens of positions already consolidated over the previous decades: he made use of Meynert’s concept of libido, the notions of auto-eroticism and narcissism of Havelock Ellis, the theory of Fliss on bisexuality and Moebius’ criticism of degeneration, in which Magnus Hirschfeld and Havelock Ellis, the theory of Fliess on bisexuality and Moebius’ of libido, the notions of auto-eroticism and narcissism of over the previous decades: he made use of Meynert’s concept theory by drawing on dozens of positions already consolidated (“paradoxia”); the clinical perversions ("paresthesia" or "paraphilias"), on which psychiatry would have increasingly concentrated in the future [53].

We have the first real and definitive departure with Kinsey who combined a statistical (psychometric) approach with a biological/taxonomic view of human sexual practices; Kinsey’s reports, in fact, which examined thousands of people who were not (apparently) psychiatric patients, found that homosexuality is more common in the general population than previously believed, although it is believed that his now famous “10 %” is closer to 1-4% and although Kinsey’s influence remained rather limited among psychiatrists in general, his evidence and arguments played an important role in the scientific discussion of how to distinguish between” normal “sexuality from the “abnormal” one [69,70].

Reflecting the general popularity of psychoanalysis in American psychiatry in the mid-twentieth century, the first two editions of the DSM were mainly inspired by
psychodynamic concepts and etiological theories [71]. The original DSM, for example, argued that sexual deviations were often symptomatic of an underlying neurological disorder or psychotic nature [72]. Similarly, other psychiatric textbooks taught that sexual perversions pursued childish sexual purposes and that all sexual perversions were to be understood as people using defenses against castration anxiety [59]. However, shortly after the release of DSM-II in 1968, the popularity of psychoanalysis began to decline between American psychiatry and the extraordinary success of early tranquilizers, such as meprobamate (Miltown) and diazepam (Valium), suggested that behind mental disorders, there could simply be psychological conflicts [71]. Finally, a growing group of “young Turks”, with solid scientific and statistical background, annoyed by the lack of systematicity within psychoanalytic psychiatry, as well as its lack of unique diagnostic rules and criteria, began a review process systematics of the DSM [73,74]. Among them, Melvin Sabshin became the medical director of the APA in 1974. Sabshin almost immediately decided almost immediately that a new edition of the DSM was needed, no longer tied to psychoanalysis but to empirical evidence. Another reason for revision was the APA’s decision to include a general definition of “mental illness” and in this the perversions, and in particular homosexuality, were not very suitable. From here, we came to understand how homosexuality had a more socio–environmental than clinical picture, in terms of personal discomfort. The 1970s were turbulent times for the American Psychiatric Association (APA). Since the Second World War, most of its members practiced psychoanalysis, but now the bewitching powers of psychoanalysis were decreasing [73,74] and this decline of psychoanalysis had laid the foundations for a new wave of psychiatric research [75,76]. Perhaps more than the 1952 DSM, the DSM–II unequivocally characterized homosexuality as a mental illness, [77] because the belief was a sort of biological and genetic programming to heterosexuality: traumatizing experiences and disturbed parent–child (or equal) relationships was thought to be able to deflect this apparently natural need, thus resulting in abnormal sexual behavior [78]. During the 1960s, however, this vision was put under attack by an ever increasing variety of factors, including gay activists and public intellectual movements [79–81], based on the theorizations of the sexologists Hirschfeld and Ellis that they supported the biological origin of homosexuality and bisexuality (as theorized by James Kiernan and Frank Lydston [82]), in antithesis with Freud. Always Hirschfeld and Ellis argued that even if heterosexuality was the natural norm, this would not explain the pathological nature of homosexuality [83]. By setting arguments to show that homosexuality was neither abnormal nor a disease, Szasz and many other members of intellectual societies supplied fuel for the work of a variety of gay activist groups. From the 1970s, some of these groups began to protest at the annual meetings of the American Psychiatric Association, where key psychoanalysts, such as Bieber and Socarides, opposed each other [84–86]. In the midst of this dispute between activists and psychoanalysts, the psychiatrist Robert Spitzer stepped forward as an intermediary and as technical consultant to the DSM–II Statistics and Statistics Nomenclature Committee, intimately supporting the pathological nature of homosexuality but at the same time suggesting an editorial compromise: being many highly functional or apparently healthy homosexuals, homosexuality had to be removed by the DSM in order to insert the morbid condition of the disturbed sexual orientation, which included those people in difficulty from their sexual orientation. A political choice, therefore, of compromise, which only apparently seems justified by clinical reasons, while nevertheless leaving a great doubt as to the technical nature of the decision. One of the fundamental clinical reasons behind this part of the proposal was an articulation of the definition of “mental disorder” which, according to Spitzer, should have two elements: “it must regularly cause subjective, stressful disorders or be regularly associated with some generalized impairment of social effectiveness or functioning.” Since many homosexuals did not fit into any of these criteria, homosexuality was not to be considered in the technical sense a “mentally ill”. However, Spitzer himself does not consider homosexuality “normal”, supporting the description of “an irregular form of real sexual development”, or “not optimal” when compared to heterosexuality. Yet suboptimal behavior, he argued, does not necessarily have to be a mess, as has been shown in examples of celibacy, racism, religious fanaticism or vegetarianism, which he jokingly described as “useless avoidance of carnivorous behavior.” [87]. In December 1973, this proposal will be accepted unanimously, albeit with the fierce opposition of the psychoanalytic community, which by asking for a referendum, lost with 42% of the votes. [84,88]. In any case, the events of 1973 did not end with the vote, as instead of homosexuality, the DSM contained a new diagnosis: “Sexual orientation disorder” (SOD). SOD viewed homosexuality as a disease if an individual with same-sex attractions found them distressing. The new diagnosis thus legitimized the practice of sexual conversion therapies (and presumably justified the insurance reimbursement even for those interventions), even if homosexuality itself was no longer considered a disease. The new diagnosis also allowed the unlikely possibility that a person dissatisfied with a heterosexual orientation could seek treatment to become homosexual. SOD was later replaced by a new category called “Ego Dystonic Homosexuality” (EDH); however, it was obvious to psychiatrists that the inclusion before SOD and later EDH was the result of previous political compromises and that no diagnosis satisfied the definition of a disorder in the new facility. Consequently, the ego–dystonic homosexuality of DSM–III was removed by the subsequent revision, in DSM–III–R, of 1987; in this way, the APA implicitly came to accept a vision that was fruitful of the normal variant of homosexuality [89,90].

**Neurobiological profiles**

Post-mortem and mass spectrometry imaging studies over the past two decades have revealed structural differences in both global and more properly brain structures related to sexuality between heterosexual and homosexual subjects [91,92].

1) **Hypothalamus:** The hypothalamus is a portion of the brain that contains a number of “nuclei” (discrete groups of cell bodies in the soma of the neuron). Now, the term “nucleus” in

neuroanatomy should not be confused with the same use that is made of it in cell biology: in the second case it refers to the organelles found in eukaryotic cells that contain the genetic material of the cell; while in the former it refers to discrete groups of neuronal cell bodies densely packed in the central nervous system. In anatomical sections, a nucleus appears as a region of gray matter surrounded by white matter. It is known to be involved in sexual differences in reproductive behavior, mediating the responses of the menstrual cycle: in particular, the anterior hypothalamus helps regulate male–typical sexual behavior. In the mid–1990s it was also linked to gender identity and sexual orientation. Seminal research conducted by Simon LeVay would have found that an interstitial nucleus of the hypothalamus, INAH3, was dimorphic according to sexual orientation but not according to gender. Specifically, the INAH3 of homosexual men was found to be of lower volume than that of heterosexual men; these results were obtained from the post–mortem analysis of hypothalamic nuclei of known homosexual subjects compared to heterosexual patients. Further research has found that INAH3 has a smaller volume in homosexual men than in heterosexual men, this because the former have a higher neuronal density within it than the latter; however, there is no difference in the number or cross–sectional area of neurons in INAH3 of homosexual men compared to heterosexuals. It has also been found that there is no effect of HIV infection on the size of INAH3, i.e. it does not take into account the observed difference in volume between homosexual and heterosexual men. The hypothalamus is also linked to sexual orientation through findings showing that aromatase activity (an important enzyme that converts androgen to estrogen) is elevated in the pre–optic hypothalamic region of the mammal during pre and neonatal. This is indeed related to sexual differentiation and may be a basis in structural and functional sexual differences that play a role in mediating the development of orientation due to prenatal hormonal exposure. The suprachiasmatic nucleus (SCN) of the anterior hypothalamus also refers to sexual orientation, being larger in size and more elongated in homosexual males than in heterosexual males and females. The cell sub–nucleus containing the SCN vasopressin of homosexual men is twice as large and has 2.1 times the number of cells compared to the sub–group containing the SCN vasopressin in heterosexual men. This could be a neurological explanation for the discovery that gay men daily wake up and retire earlier than heterosexuals, since SCN is known to be involved in modulating human circadian rhythm. Similarly, in a rat model study, male rats treated with an aromatase inhibitor were found to show a preference for females when tested in the late stage, but showed preference for homosexual mating when instead tested in the first dark phase, implying the involvement of the SCN in orientation in other species [93–96].

2) Thalamus: The thalamus is a symmetric ovoid structure of the midline within the human brain, located between the cerebral cortex and the midbrain in both cerebral hemispheres. A magnetic resonance imaging study compared subcortical volumes of homosexual and heterosexual men; he found that while both groups did not differ in total brain volume, the volume of the thalamus (in both hemispheres) was greater in heterosexual men. Another study reported that functional connectivity involving the right thalamus and right cuneus was different between homosexual and heterosexual men and also showed correlations with the Kinsey scale scores; also the thalamus is involved in the process of sexual arousal and reward; during the visually evoked excitement both heterosexual men and homosexuals activated the thalamus, but in contrast to the latter, heterosexuals showed further activation in the lingual gyrus [97,98].

3) Basal nucleus of the stria terminalis: The basal nucleus of the terminal stria (BNST) is an area of the limbic system of the forebrain which is involved in the control of mating behavior; it receives neuronal inputs from the medial amygdala and the accessory olfactory bulb and sends projections to both the medial pre–optic area and the ventro–medial nucleus of the hypothalamus. The central part of the BNST (the BNSTc) is 44% greater in heterosexual men than straight women and 62% greater in homosexual men than the same. The BNSTc is larger in homosexual men than in straight men, although the difference in size is not statistically significant. It is therefore assumed that the BNSTc of homosexual men is “hyper–masculinized” as it is larger than the BNSTc of straight men and women [99–101].

4) Amygdala: Both men and homosexual women have connections to the amygdala other than those of heterosexual men and women. Specifically, the connections between homosexual men and straight women were more common in the left amygdala, while in straight men and lesbians functional connections were more common in the right one [102,103].

5) Front commissure: It is a bundle of white matter fibers that connects the two cerebral hemispheres, it was found by Allen and Gorski to be significantly wider in homosexual men and in heterosexual women than in heterosexual men [97]. This finding provides a possible anatomical basis for higher inter–hemispheric functional connections in homosexuals, which explain why homosexual men and heterosexual women show a marked functional symmetry of the language circuit in comparison to heterosexual men performing the same tests verbal [104].

6) Corpus callosum: The corpus callosum (CC), as well as the anterior commissure, is an important neuronal connection that connects the two hemispheres; however, unlike the commissure (which is present in all types of vertebrates), CC is present only in placenta animals [101] An MRI study that compared the CC of homosexual and heterosexual men found that all parts of the CC are larger in homosexual people. [102] In particular, the isthmus (a part of the CC present between the corpus callosum and the splenium muscle of the head) is significantly larger in homosexual men than in heterosexuals; [105,106] the size of the CC has a strong genetic basis, with genetic inheritance rates between 82 and 94%. [107] This association of sexual orientation with a highly heritable brain structure supports the thesis of a genetic and neurobiological basis in the origin of the same orientation [105].

7) Gray substance: Gray matter is an important part of the
central nervous system which is mainly composed of neuronal cell bodies. While men generally have a greater amount of gray and white matter than women, due to the greater male body mass and consequently a greater brain size, women generally have a greater gray matter–matter ratio and thicker layers of it in specific areas of the cerebral cortex compared to men. [101,107]. Homosexual women have been found to have relatively less gray matter than straight women in the ventral cerebellum area, the left ventral premotor cortex, the temporo-basal cerebral cortex and, more significantly, the perirhinal cortex left of the temporal lobe. No difference in the amount of gray matter was found between straight and homosexual men [107]. These results are important because the perirhinal cortex is located near the brain regions (entorhinal cortex, hippocampus, parahippocampus gyrus and amygdala) involved in olfactory and spatial processing, which have been shown to determine differences in sexual orientation (in particular, performance in homosexual women is superior to straight women in spatial processing tests) [104,107]. The perirhinal cortex itself is involved in functions related to the processing of sexual stimuli such as olfactory processing, memory coding and spatial processing itself; it is also involved in detecting the identity of the object. It is known that it changes sexual attraction in humans and the olfactory system is able to differentiate pheromone-like compounds based on sexual orientation. The discovery that homosexual women have a “male” GM model while homosexual men do not have a “female” model indicates that male homosexuality and lesbianism do not manifest themselves structurally in the brain. In addition, other findings of sexually dimorphic characteristics that are more masculine in homosexual women, but not feminine in homosexual men, include otococinac emissions, the 2D:4D finger ratio and build. Overall these results suggest that atypical sexual levels of prenatal androgenic action may be involved in the origin of female homosexuality [107].

8) Hemispheres and cerebral cortex: The size of the telencephalon is a sexually dimorphic trait in which men tend to show asymmetry in the volumes of their hemispheres, while women instead show a volumetric symmetry. It is also a trait that is highly unlikely to be influenced by learned socio–environmental patterns [103]. A volumetric magnetic resonance study indicated that homosexual men and heterosexual women showed symmetrical hemispherical volumes while homosexual women and straight men showed asymmetry to the right. These results demonstrate a global neurological difference in brain structures showing atypical sexual characteristics associated with sexual orientation [108]. The cerebral cortex, which is the outermost layer of the human brain and composed of nerve tissue, offers other food for thought. An MRI study compared the cortical thickness in various brain regions of homosexual men, heterosexual men and heterosexual women: it found that homosexual men had thinner cortices –compared to straight ones– in the lateral orbital–frontal region of the right hemisphere, as well as in the regions located in the visual cortex (lingual, pericalcarine and wedge). The same regions showed a thinner cortex in heterosexual women than straight men, while no differences were found between heterosexual women and homosexual men. Homosexual and straight males did not differ in total brain volumes and it was determined that the differences reported in cortical thickness were not influenced by the years of education or the brain volume of the subjects. Since the regions mentioned above show sexual dimorphism, the authors hypothesized that the biological processes frequently proposed to underestimate the same, such as the mechanisms dependent on the gene and sexual hormone during prenatal and postnatal development, may interact with cortical architecture in visual areas resulting in different cortical thicknesses in homosexuals compared to hetero. Furthermore, homosexual men showed thinner cortices than straight men and women both in the triangular pars right (also known as Brodmann area 45 and in the lower temporal regions; this suggests that brain differences related to male homosexuality may also be present in regions that are not necessarily considered as sexual dimorphic. Even more evident are the differences with the brains of transsexuals: the pars triangularis of MtF transsexuals (and heterosexual men) is thicker than that of gays; moreover in MtF transsexuals it is also thicker than in straight men. In particular, in both studies, the region concerned is the pars triangularis present in the right hemisphere [109].

Functional differences

In particular, two human pheromones were investigated – the progesterone derivative 4,16-androstdien-3-one (AND) and an ester–1,3,5 (10), 16-tetraen-3-ol (EST) (estrogen-like steroid – demonstrating specific responses to sexual orientation in the activation of the neural circuits of the anterior hypothalamus in both homosexual and heterosexual subjects. The anterior hypothalamus is involved in the elaboration of reproductive functions and recent evidence suggests that it helps to integrate the hormonal and sensory stimuli involved in sexual behavior and its preferences. Recent functional magnetic resonance imaging experiments have shown that the presentation of AND, found in male sweating, as an olfactory stimulus produced normal olfactory responses in straight and lesbian men, while activated the anterior hypothalamus in homosexual men and straight women. The EST proposal of the pheromone, found in the urine of pregnant women, produces a hormonal olfactory activation in gay men and heterosexual women, while on the other hand lesbians and straight men have been shown to have sexually related hypothalamic responses. Gay men showed the same sexually related functional responses to these stimuli as heterosexual women, while homosexual women responded as straight men. This research conducted by Berglund and Savic indicates overall that AND and EST induce “specific effects of sexuality on the autonomic nervous system” and that the stimuli produced a response path that depended on the subject’s sexual orientation rather than on the sex resulting from the phenotype [104,110].

With reference to the response to sexual stimuli, some premises must be made. Sexual arousal is a highly coordinated process that prepares a person for reproductive behavior; diffuse changes occur in the person’s neurophysiological state during arousal to obtain adaptive responses. The attention, affective and motivational systems of the individual concerned are optimized
in such a way as to allow the selection and successful use of sexual stimuli. In response to visual sexual stimuli, men show specific category subjective and self-reported excitement; their greatest excitement is directed to those categories of people with whom they prefer to have sexual intercourse: homosexual men experience greater genital and subjective arousal for men than for women (and therefore prefer male sexual stimuli), while for heterosexual men the reverse occurs. In the prenatal period, the hormone is believed to influence the development of the neural structures that regulate sexual behavior; therefore it is believed that some aspects of neurohormonal development in homosexuals proceed differently from heterosexuals, with consequent psychological differences such as distinct triggers (or “stimuli”) for sexual arousal. A 2007 study explored the neural mechanisms of sexual arousal in homosexual and straight men, demonstrating that both male groups activated the same brain regions after each was exposed to a sexual stimulus consistent with the sexual orientation of the subject under consideration [111]. Another fMRI study showed that by observing both heterosexual and homosexual erotic visual stimuli, only those videos corresponding to the subject’s sexual orientation produced activation patterns in the areas of the brain associated with sexual arousal. The response of heterosexuals showed the same pattern of neural sexual processing which caused homosexual vision, while the visualization of the images of the opposite orientation did not elicit the same response. A significant correlation was therefore found between excitement and neural activation in the hypothalamus, a key region of the human brain for its sexual function; self-reported sexual arousal values were also the same in both groups. However, the extent of hypothalamic activation was lower in homosexual men than straight men, a trait that is also shared by straight women [112]. A further fMRI study determined brain activation patterns in homosexual and heterosexual subjects, exposing them to homosexual and heterosexual visual stimuli; they therefore found that different neuronal circuits were active in the two male groups: brain regions such as the left angular convolution, the right pale globe and the nucleus of the left caudate were activated exclusively in homosexual men while the bilateral lingual gyrus, the parahippocampal right gyrus and the Right hippocampus were activated exclusively in heterosexual men. These results indicate that the neural circuits (related to the processing of visual sexual stimuli) that are active during sexual arousal in homosexual and heterosexual men are different. [113] New fMRI research showed heterosexual and homosexual women and men photos of male genitalia and female genitalia; therefore, by limiting the visual sexual stimulus to the photographs of the genitals, the authors have reduced to a minimum the neuronal activity related to the processing of various stimuli such as faces, voices, body movements and sexually exciting parts of the body in addition to the genitals. They found that the ventral striatum, the centromedian thalamus, and the bilateral ventral premotor cortex showed a stronger response to photos of favorite sex than the corresponding photos of not-preferred sex. Since the ventral striatum and the centromedian thalamus are known to be activated by innate preferences, the selective response of these regions to preferred sexual stimuli seems to reflect a predetermined response pattern. This notion is therefore used as a support for one of the tests that want sexual orientation to be of purely biological origin [114]. Another fMRI study sought to verify whether the subjects responded more to the faces (male or female) to which they were sexually oriented and predicted such modulation in the brain circuit of the reward system. Heterosexual and homosexual men and women were shown photos of male and female faces and therefore invited to evaluate their visual attractiveness. Consistent with the hypothesis, it was discovered that the reward circuit of homosexual males and heterosexual females responded more to photographs of male faces, while the reward circuits of homosexual females and heterosexual males responded more to photographs showing female faces. The interaction between stimulus gender (male or female face) and sexual orientation (homosexual or heterosexual) of the subject was highly significant in two brain regions: the mid-dorsal thalamus nucleus (MDT) and the medial orbitofrontal cortex (OFC). Activation in the OFC is notable because it is involved in representing the reward value of various sensory stimuli, including attractive faces. It also appears to have an important role in the processing of facial signals necessary for social communication, since this region has selective neurons for the face and because patients with OFC lesions are unable to identify emotional facial expressions [115].

Again in relation to sexual orientation, significant differences were found in neural processing and cognitive tasks. In a 1987 review of cognition, cerebral lateralization and orientation, Sanders and Ross–Field suggested that prenatal hormonal events would lead to functional brain asymmetries related to the same orientation. Since that date, hundreds of studies have taken turns to confirm this thesis. Some cognitive tasks are known to be sexually dimorphic. The better verbal ability of women is associated with a reduced lateralization of language activities, while the male advantage in spatial tasks corresponds to the marked cerebral lateralization. Effects of sexual orientation in some of these tasks have been noted in several studies. In the Vincent Mechanical Diagrams test, a measure of the split point detection field of functional brain asymmetry, gay men achieved the same result as heterosexual women and both with lower scores than straight men who showed less asymmetry. In addition, homosexual men show IQ scores for verbal performance higher in the sub–tests of the Wechsler Adult Intelligence Scale, in accordance with the test models performed by women. In many other tests, which included a targeted launch task by the male and one of the neuropsychological tests (the “Purdue Pegboard”) with female partiality, the performance of homosexual men and straight women showed no significant statistical difference from each others, while both differed significantly from heterosexual men. Furthermore, a reduction in asymmetry was found in a magneto–encephalographic study in which it is found that the localization estimates of origin of an auditory signal evoked by MEG are hemispherically symmetric in heterosexual women and homosexual men, while they are asymmetric in men hetero [116].

Serotonin studies also present very interesting elements. Serotonin is a neurotransmitter found in the central nervous
system that has various roles in regulating sexual behavior; its agonists and antagonists have activating or inhibiting effects depending on their concentration and the brain area involved. Fluoxetine is a selective serotonin reuptake inhibitor that prolongs the effect of serotonin on neurons [117]. Kinnunen and others administered fluoxetine to their study subjects to see if the brain is activated in a different way in homosexual and heterosexual men through the action of serotonin; after administration of fluoxetin they measured glucose (fluorodeoxyglucose) metabolism in the brain using positron emission tomography (FDG-PET). They found that the brain response to fluoxetine differs between gay people and straight men, i.e. the former show less reduction of glucose metabolism in the hypothalamus than the latter. In addition, other areas of the brain were also activated differentially: the prefrontal associative cortex of homosexual men showed greater activity after administration, while that of straight men showed no change. The cuneus gyrus, the anterior lateral girdle, and the bilateral hippocampus / parahippocampal gyrus of straight men showed greater activity, while reduced portions of their anterior cingulate cortex were observed. These results suggest that homosexuals and heterosexuals may not only differ in the total number of neurons in various areas of their central nervous system, but may also differ in the distribution of certain types of them, such as serotonergic and dopaminergic neurons [101,18].

Conclusions

The topic under consideration is very thorny, more for its socio-political implications than clinical ones.

Discussing the reasons for a correct inclusion or exclusion of this category in the DSM certainly represents both an excellent exercise of nomenclature, in order to also verify the quality and validity of a definition of mental illness, and to better define the related clinical picture in relation to the anamnestic profiles of the patient. In this context, it is necessary to omit the socio-political and anthropological aspects, and all the possible legal repercussions determined by the hypothesis confirming homosexuality as a mental pathology. In fact, there is no judgment of merit or form at stake here, as much as the exact clinical location in the cognitive and experiential sphere of the mental health professional. These considerations are completely detached and far from any form of ethical, moral, social and personal judgment or condemnation; at most, the intention is to make a de facto contribution to the clinical cause, trying to overcome any preconceptions and prejudices typical of a dysfunctional social subculture reaching out towards the isolation and ghettoization of the homosexual or bisexual person. Net from a position contrary to personal freedom, the sacrosanct civil rights struggles of the last decades are welcome, to recognize equal conditions and not discriminate against any person regarding their sexual choice. Here, therefore, at stake, there is no condemnation of a category but simply the stance of a strictly clinical evaluation, also in light of the neurobiological results of recent years.

Research on the relationship between neuroscience and sexual orientation is still in its infancy, despite the numerous progress made and the finding of substantial elements capable of supposing that the neuroanatomophysiology of a not-heterosexual subject is different from a heterosexual subject. However, to date, studies have not yet clarified whether it is these differences that cause different sexual orientation or whether orientation (learned through social conditioning or genetic predisposition) shapes the anatomy and physiology of the brain by inducing the changes. It is logical and consequential to think, however, that the first solution is the most acceptable and therefore some anatomical-physiological alterations cause the subject to perceive his orientation as “not-heterosexual”.

On this hypothesis, still to be verified, the suspicion remains that the decision to “reroute” homosexuality and bisexuality – making them become normal and sexual orientations, such as heterosexuality - can be considered forced (based on more social and political pressures, which are strictly clinical), in the light of the various neurobiological findings that have emerged in research over the past thirty years. Excluding the social and legal implications, thus suspending any moral and ethical judgment on the various positions of sexual orientation, the need to better contextualise the clinical profiles relating to the topic under examination appears interesting. More than interesting, the analyzes regarding these directly related aspects appear, contextualising:

- any differences between the “homosexual tendency” (determined perhaps by paraphilic [119] or post-traumatic adaptive factors [120]) and the precise and conscious decision to perceive one’s balance in the “homosexual or bisexual condition” (therefore the de facto choice of orientation) [121];

- any that allow to clearly distinguish comorbid conditions (such as anxiety disorders, eating disorders, depressive disorders, panic, obsessions, behavioral addictions and suicidal risk) [122-129], from the choice homosexual or bisexual (and whether the latter is able to feed the comorbid conditions);

- the differences between highly adaptive and functional conditions from those that cause the patient to feel unwell and dysfunctional.

With regard to this last point, in particular, it is really important to underline that the high functionality of the patient, with regard to his homosexual or bisexual condition, more or less definitive, does not in itself exclude that it is not pathological compared to the heterosexual condition. The possible hypotheses at stake are essentially four [1]:

- heterosexuality is the only orientation considered normal, depending on the physical and genetic predisposition and reproductive biology of individuals. Therefore, any other condition other than heterosexuality, albeit highly adaptive, represents a clinical condition worthy of evaluation;

- heterosexuality is the only orientation considered normal, depending on the physical and genetic predisposition and reproductive biology of individuals. Therefore, any other condition other than heterosexuality, albeit highly adaptive, represents a clinical condition worthy of evaluation only if the patient perceives his condition as dysfunctional (or ego-dystonic);
heterosexuality and homosexuality are the guidelines considered normal, according to the social adaptation of individuals. Therefore, only bisexuality is a clinical condition worthy of evaluation, even if highly adaptive, as it is the result of a basic paraphilic condition that prevents the subject from making a precise orientation choice.

heterosexuality is not the only orientation considered normal, according to the social adaptation of individuals. Therefore, any other condition other than heterosexuality, whether homosexual or bisexual, provided it is highly adaptive, does not represent a clinical condition worthy of evaluation. If the condition causes maladaptation, this must be psychologically reworked, to find a balance and allow the patient to become highly functional; in the latter case, however, the homosexual or bisexual choice does not have a clinical origin and it is any pre-existing psychopathological conditions that determine the patient’s perceived malaise.

Neurobiology, however, is clear on the point (although researchers have a prudent attitude for fear of legal and professional repercussions), especially with reference to the altered functionality and structure of the hypothalamus, thalamus, basal nucleus of stria terminalis, Amygdal, corpus callosum, gray matter, hemispheres and cerebral cortex [93-120], and if homosexuality and bisexuality present neurobiological dynamics other than heterosexuals, also considering the reproductive biological structure (reproduction is possible only between subjects who present opposite and complementary sexual systems), the re-evaluation of the decisions that led to the derubrication of homosexuality and bisexuality as healthy and alternative forms of sexual orientation, deserves a clinical study.

In the future, research should focus on the following investigation points:

a) studies aimed at distinguishing paraphilic forms from definitive orientation choices;

b) studies aimed at finding any differences between heterosexual, homosexual and bisexual subjects with reference to brain structures and the levels of serum markers of sexual steroids, both in fetuses and in adults, in all its evolutionary development, thus highlighting any conditioning in able to lead to certain sexual orientation choices other than heterosexuality;

c) studies able to determine the precise direction of the neural circuits underlying sexual preferences, comparing the results with heterosexual subjects;

d) studies able to focus research on genetic factors capable of influencing sexual orientation.

The direct and indirect implications on the confirmation of the clinical hypothesis of the homosexual and / or bisexual condition would bring further complications, with reference to the management of the patients’ treatments and therapies, while making important differences between highly adaptive patients and those who perceive their condition as dysfunctional with respect to the surrounding environment.

The question to ask, in this theoretical hypothesis, is whether we must actually intervene clinically to correct the homosexual or bisexual condition and lead the patient towards a heterosexual orientation, or simply accompany him towards a better perception of his emotions, desires and needs. Strategically [130,131]. What seems certain is that the static and nosographic evaluation of “mental illness” in reference to homosexuality or bisexuality is not at stake, the more the awareness of a clinical reality with respect to the topic treated and the evaluation by the therapist of any anamnestic profiles related to high adaptive functionality or to the patient’s ego-dystonic and dysfunctional perception.

The confirmation of the clinical nature of homosexuality and bisexuality could also revive or reawaken the theses set aside in the last century on possible therapies aimed at correcting dysfunctional sexual orientation, through psychotherapy (mainly post-Freudian dynamic orientation) or the use of neurostimulating equipment (for example electroshock), with a whole series of ethical, moral, social, political and psychological implications that are not indifferent to the daily needs of the patients.

These profiles must necessarily be directed to the appropriate research sites, carefully evaluating the patient’s medical history and whether his or her choice of sexual orientation is experienced or not by the patient in a highly adaptive or dysfunctional way.

Neurobiological evidence, in tune with socio-cultural and political positions, underlines the need to consider clinical hypotheses related to not-heterosexual preferences, with a whole series of exceptions. In general, even if the clinical nature of the not-heterosexual choice proves, this condition should not in itself justify treatments contrary to the dignity and will of the person. The scientific evidence received so far is not definitive and deserves further investigation to reach meaningful conclusions capable of determining collective awareness.

References


38. Gall FJ (1835) On the functions of the brain and each of its parts: With observations on the possibility of determining the instincts, propensities, and talents, of the moral and intellectual dispositions of man and animals, by the configuration of the brain and head. Boston: Marsh, Capen, Lyon. Link: https://bit.ly/2MKRfBQ


65. Tripp CA (1975) La matrice omosessuale. Meridiano; New York, NY, USA.


90. Snell RS (2010) Clinical Neuroanatomy. 7th, Lippincott Williams & Wilkins 34.


